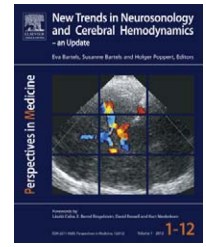
Perspectives in Medicine (2012) **1**, 39—43

Bartels E, Bartels S, Poppert H (Editors):
New Trends in Neurosonology and Cerebral Hemodynamics — an Update.
Perspectives in Medicine (2012) 1, 39—43

journal homepage: www.elsevier.com/locate/permed



Relationship between refill-kinetics of ultrasound perfusion imaging and vascular obstruction in acute middle cerebral artery stroke

Manuel Bolognese*, Dimitrios Artemis, Angelika Alonso, Michael G. Hennerici, Stephan Meairs, R. Rolf Kern

Department of Neurology, UniversitätsMedizin Mannheim, University of Heidelberg, Mannheim, Germany

KEYWORDS
Ultrasound perfusion imaging;
Refill kinetics;
Ischemic stroke;
Microbubbles

Summary
Background: Ultrasound perfusion imaging (UPI) with bolus kinetic has been shown to be feasible at bedside for evaluation of perfusion deficits in stroke patients. Recent technical advances allow perfusion imaging with refill kinetics using a low mechanical index.
Methods: We examined 31 acute middle cerebral artery (MCA) stroke patients with transcranial color-coded duplex ultrasound (TCCD) and UPI. The refill of microbubbles was calculated from regions of interest in the ischemic area and the contralateral MCA territory by using the exponential function $y = A(1 - e^{\beta t})$; A = acoustic intensity of the plateau (dB), β = slope (1/s).
Results: We found significantly lower values of β in the ischemic area compared with the contralateral MCA territory (0.75 vs. 1.05 1/s, $p < 0.05$); particularly in patients with a pathological MCA flow pattern on TCCD (0.61 vs. 1.01, $p < 0.01$). There was a high interindividual variance without significant difference of the plateau of acoustic intensity (A) in any subgroup of patients.
Discussion: The slope parameter β of refill kinetics is useful for assessing brain perfusion in patients with acute stroke and pathological flow pattern of the ipsilateral MCA. The parameter A, however, seems more dependent from the quality of the temporal bone window.

Introduction

Assessment of cerebral perfusion is highly relevant for the immediate diagnostic work-up of acute ischemic stroke. MRI and CT perfusion are routinely used to identify patients who may benefit from recanalizing therapy beyond the standard time window, identifying salvageable tissue at risk of infarction by the MR diffusion-perfusion-based mismatch concept [1]. Other perfusion imaging methods like PET-CT and SPECT are not feasible in acute stroke patients because of logistic limitations.

Ultrasound perfusion imaging (UPI) has been shown to be able to likewise identify perfusion deficits of the brain parenchyma [2—4]. The advantages of UPI are the possibility to perform and repeat the examination at patient's bedside, allowing a non-invasive, cheap and quickly applicable assessment of cerebral perfusion on an intensive care unit or a stroke unit.

* Corresponding author at: UniversitätsMedizin Mannheim, University of Heidelberg, Department of Neurology, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel.: +49 621 383 2885.
E-mail addresses: bolognese@neuro.ma.uni-heidelberg.de, manuel.bolognese@gmx.de (M. Bolognese).

2211-968X © 2012 Elsevier GmbH. Open access under CC BY-NC-ND license.
doi:10.1016/j.permed.2012.01.004

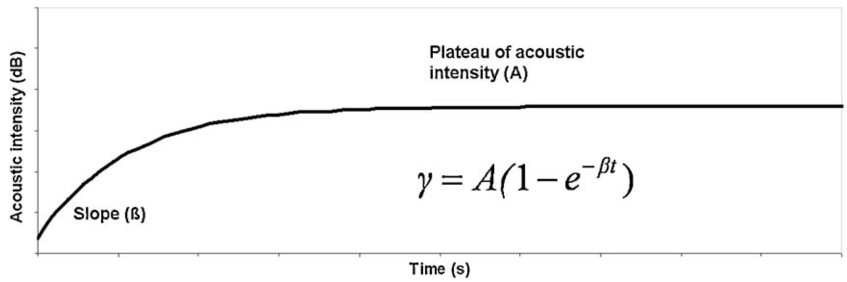


Figure 1 Exponential function of microbubbles replenishment after destruction of microbubbles. γ is the acoustic intensity measured at pulse interval t, A represents the plateau of acoustic intensity during refill kinetic and β is the slope of the acoustic intensity over time.

The main limitations of this method are the attenuation of ultrasound by the human skull and the interindividual variance of skull thickness [5]. In order to guarantee a sufficient penetration of ultrasound, a high ultrasound energy (high mechanical index = MI) was necessary in earlier UPI protocols. This led, however, to an early destruction of the echo-contrast agent microbubbles, which made it necessary to trigger the ultrasound impulses with a frequency of 1—2/s. This resulted in a relevant decrease of the temporal resolution of UPI and thus of the sensitivity of this method to detect small differences of cerebral perfusion between different regions of interest (ROI) [6].

Recent advances in ultrasound technology now allow to perform UPI using low ultrasound energy (i.e. low MI), which enables perfusion studies in real time (rt-UPI) without the need of triggering the impulses, leading to improved temporal resolution [7]. Bolus kinetics, where the time after application of the ultrasound contrast agent until the maximum of acoustic intensity (=time to peak) is measured, has been already established as a valid method to assess human brain perfusion with ultrasound [4]. Another interesting method to measure tissue perfusion with UPI is refill kinetics, which has been first used by Wei and coworkers in myocardial tissue [8]. After injection of echo-contrast agents, the circulating microbubbles in the ultrasound plane are destroyed by a repetitive ultrasound pulse with high MI, followed by registration of the replenishment of microbubbles in the cerebral microvasculature with low MI. The replenishment can be demonstrated by an exponential equitation $y = A(1 - e^{\beta t})$, where A represents the plateau of the acoustic intensity and β the slope factor of the exponential curve (Fig. 1).

Refill kinetics has been also employed successfully to measure cerebral perfusion in an animal model of trepanated dogs, showing a good correlation with cerebral blood flow [9]. We have recently reported that refill kinetics is also feasible for assessing cerebral perfusion in acute middle cerebral artery (MCA) stroke patients [10]. In the present study, we investigated the relationship between the rt-UPI parameters of refill kinetics and the degree of underlying arterial obstruction of the MCA as assessed by transcranial color-coded duplex ultrasound (TCCD).

Methods

We used a Philips IU 22 system and a 1—5 MHz sector transducer for rt-UPI and TCCD studies. Inclusion criteria were sufficient transtemporal bone windows bilaterally and a territorial acute MCA stroke as shown by either CT or MRI. Exclusion criteria were any contraindication against SonoVue®, a second-generation ultrasound contrast agent based on sulfurhexafluoride microbubbles [11].

TCCD and rt-UPI studies were performed within the first 24 h after onset of stroke. TCCD was used to evaluate the quality of the temporal bone window. The maximum systolic flow velocity of the MCA was measured in different depths bilaterally (Fig. 2). The severity of vascular obstruction was expressed by the COGIF grades [12] indicating different degrees of persistent arterial obstruction (COGIF grades 0—3) or residual stenosis/reperfusion (COGIF grade

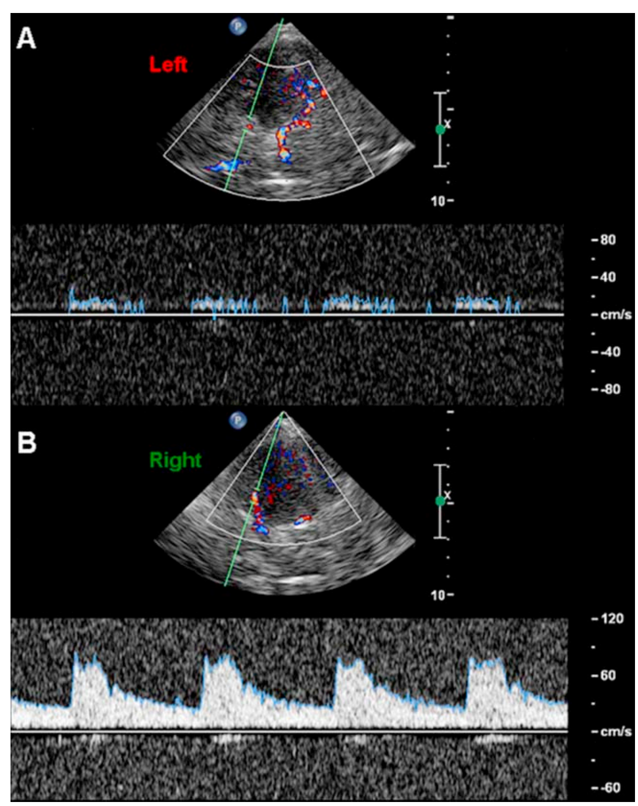


Figure 2 Example of patient with left middle cerebral artery (MCA) stroke: TCCD of the left (A) and right hemisphere (B) showing an occlusion of the proximal left MCA (COGIF-Score 2) and a normal flow pattern of the right MCA.

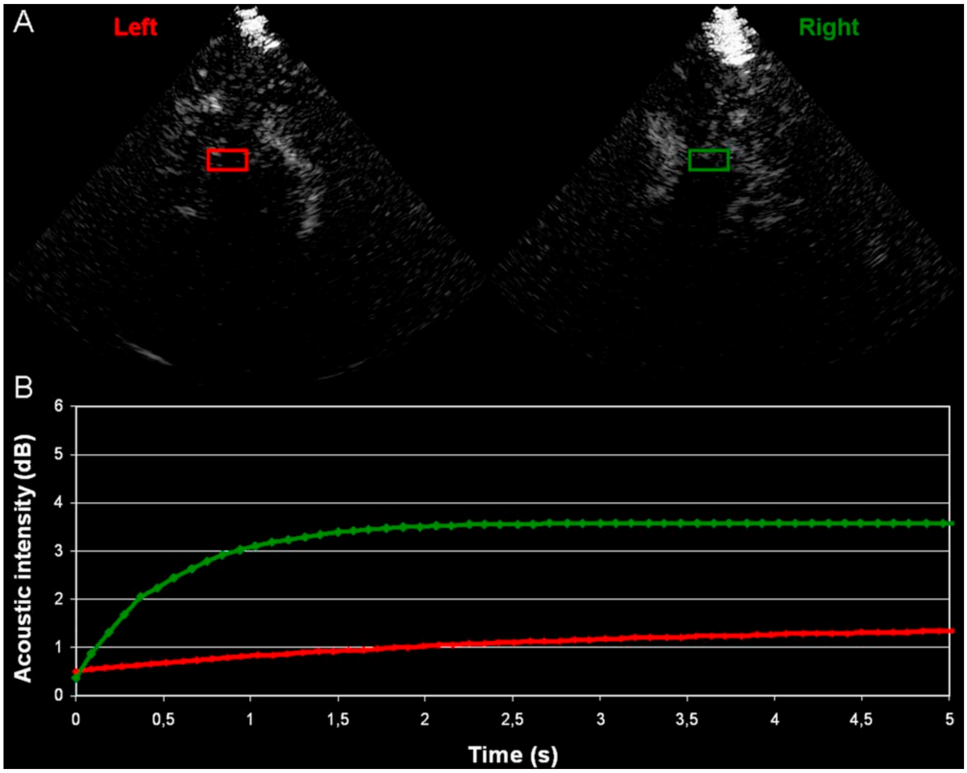


Figure 3 Real time ultrasound perfusion imaging (rt-UPI) of both hemispheres (A) with corresponding regions of interest in the ischemic area of the left (red) and the contralateral MCA territory (green). Refill kinetics (B) show a flattened curve with low slope of the exponential function in ischemic tissue (red), and a normal replenishment of microbubbles in the contralateral hemisphere (green).

4). For rt-UPI the ultrasound plane was tilted 20° cranially from the mesencephalic plane, displaying lateral and third ventricle and the thalamus. A bolus of 2.5 ml Sonovue® was injected and parameters of refill kinetics were calculated from selected ROIs in the ischemic area under avoidance of large vessels. After 10 min, we examined the contralateral hemisphere with the same protocol. We selected ROIs in the contralateral MCA territory, which corresponded in size, shape and localization to the ischemic ROIs (Fig. 3). Parameters of refill kinetics (A, β and the product $A \times \beta$) were extracted from each ROI for statistical analysis. To analyze the potential relationship between MCA flow velocity and the parameters of refill kinetics, we subdivided patients in two groups: patients with persisting MCA pathology defined by COGIF grades of 3 or lower, and patients with symmetrical or increased MCA flow (COGIF grade 4).

Results

We examined 31 patients (17 male, 14 female, mean age 68.3 ± 13.4) who were admitted to our stroke unit with acute ischemic stroke in the MCA territory (Table 1). 58% of patients were treated with intravenous thrombolysis. At the time point of examination, TCCD showed a persistent pathological flow pattern of the ipsilateral MCA (COGIF grades 0—3) in 21/31 (67.7%) patients. Pathological flow patterns were more frequent among patients who were not treated with tPA (11/13 vs. 10/18, $p = 0.08$). Rt-UPI showed significantly lower values of the refill parameter β in the ischemic area compared to the contralateral MCA territory (β (1/s): 0.75 ± 0.41 vs. 1.05 ± 0.51, $p < 0.05$). The difference between ischemic and contralateral ROIs was more prominent in patients with persisting MCA obstruction ($n = 21$; β (1/s): 0.61 ± 0.31 vs. 1.01 ± 0.53, $p = 0.005$). Correspondingly, in patients with symmetrical or increased ipsilateral MCA flow, β values were not significantly different between both hemispheres ($n = 10$; β (1/s): 1.04 ± 0.47 vs. 1.14 ± 0.49, p = n.s.). There was no significant difference between β values of the ischemic tissue of patients treated with tPA and those who did not receive systemic thrombolysis (β (1/s): 0.72 ± 0.32 vs. 0.78 ± 0.53, p = n.s.). For the plateau of acoustic intensity (A) and the product of A and β ($A \times \beta$), there was a high interindividual variance of the values, resulting in no significant difference between ischemic or contralateral healthy tissue in any group of patients (Table 2).

Discussion

This study investigated the feasibility of rt-UPI with refill kinetics to assess perfusion deficits related to persistent or already recanalized arterial obstruction in acute MCA stroke patients. The parameter β, which represents the slope factor of the exponential function of refill kinetics, shows overall significant differences between ischemic and healthy tissue. This finding was more pronounced in patients

Table 1 rt-UPI parameters and COGIF grades of the ipsilateral MCA as assessed by TCCD.

	COGIF grade (ipsilateral MCA)	Ischemic tissue			Normal tissue		
		A	β	$A \times \beta$	A	β	$A \times \beta$
1	4	2.78	1.83	5.09	9.33	1.05	9.80
2	3	1.66	0.92	1.53	4.24	0.67	2.84
3	4	0.35	0.61	0.21	0.17	0.69	0.12
4	3	1.13	0.33	0.37	1.64	0.61	1.00
5	3	1.8	0.82	1.48	1.9	2.2	4.18
6	4	1.08	0.81	0.87	1.97	0.67	1.32
7	4	2.57	1.17	3.01	2.36	1.36	3.21
8	1	7.58	0.04	0.30	6.06	1.47	8.91
9	3	1.79	0.63	1.13	0.5	0.96	0.48
10	3	0.99	0.68	0.67	0.86	1.17	1.01
11	1	3.92	0.3	1.18	3.89	0.86	3.35
12	4	0.51	0.67	0.34	2.29	2.24	5.13
13	3	4.26	0.5	2.13	2.58	1.22	3.15
14	3	1.13	0.87	0.98	0.93	0.89	0.83
15	4	2.66	0.63	1.68	3.99	0.88	3.51
16	4	2.98	1.66	4.95	0.76	1.45	1.10
17	4	3.15	1.51	4.76	1.23	0.88	1.08
18	3	0.77	0.82	0.63	1.42	0.63	0.89
19	3	6.18	0.63	3.89	13.37	0.41	5.48
20	4	10.22	0.75	7.67	13.17	1.43	18.83
21	3	2.37	0.39	0.92	3.4	0.48	1.63
22	4	3.81	0.74	2.82	5.53	0.78	4.31
23	3	2.86	1.31	3.75	0.89	1.26	1.12
24	1	20.2	1.11	22.42	3.88	0.95	3.69
25	3	1.46	0.44	0.64	20.75	0.66	13.70
26	2	20.3	0.58	11.77	1.95	1.23	2.40
27	3	24.83	0.28	6.95	12.43	1.94	24.11
28	2	0.97	0.39	0.38	3.22	1.85	5.96
29	3	2.42	0.78	1.89	0.59	1.08	0.64
30	3	0.78	0.29	0.23	0.72	0.28	0.20
31	1	0.01	0.62	0.01	0.4	0.33	0.13

Table 2 Mean values of rt-UPI parameters and subgroup analysis according to the degree of vascular obstruction.

	All patients			COGIF 0—3			COGIF 4		
	Ischemic tissue	Normal tissue	p-Value	Ischemic tissue	Normal tissue	p-Value	Ischemic tissue	Normal tissue	p-Value
A	4.44 ± 6.20	4.08 ± 4.84	n.s.	5.11 ± 7.26	4.08 ± 5.22	n.s.	3.01 ± 2.79	4.08 ± 4.18	n.s.
β	0.75 ± 0.41	1.05 ± 0.51	<0.05	0.61 ± 0.31	1.01 ± 0.53	0.005	1.04 ± 0.47	1.14 ± 0.49	n.s.
$A \times \beta$	3.05 ± 4.48	4.33 ± 5.67	n.s.	3.01 ± 5.23	4.08 ± 5.65	n.s.	3.14 ± 2.45	4.84 ± 5.66	n.s.

with COGIF grades 0—3 and was absent in COGIF grade 4. The parameters A and the product $A \times \beta$ showed high standard deviations in our study, which resulted in a lack of significance between ischemic and non-ischemic tissue for these parameters. The most likely reason for the failure of establishing the plateau of acoustic intensity as a reliable parameter of rt-UPI is the strong relationship between the acoustic intensity and the individually varying level of acoustic attenuation by the temporal skull bone. Reliable mathematical algorithms developed to estimate the level of attenuation of ultrasound by the human skull may improve the diagnostic confidence of these parameters in future.

Conclusion

The slope parameter β of refill kinetics is useful for the assessment perfusion deficits in the acute phase of MCA stroke. According to our data, the severity of the perfusion deficit as measured with β is strongly related to the underlying vascular pathology of the ipsilateral MCA.

References

[1] Schellinger PD, Thomalla G, Fiehler J, Kohrmann M, Molina CA, Neumann-Haefelin T, et al. MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients. Stroke 2007;38:2640—5.
[2] Kern R, Perren F, Schoeneberger K, Gass A, Hennerici M, Meairs S. Ultrasound microbubble destruction imaging in acute middle cerebral artery stroke. Stroke 2004;35:1665—70.
[3] Seidel G, Albers T, Meyer K, Wiesmann M. Perfusion harmonic imaging in acute middle cerebral artery infarction. Ultrasound Med Biol 2003;29:1245—51.
[4] Seidel G, Meyer-Wiethe K, Berdien G, Hollstein D, Toth D, Aach T. Ultrasound perfusion imaging in acute middle cerebral artery infarction predicts outcome. Stroke 2004;35:1107—11.
[5] Deverson S, Evans DH, Bouch DC. The effects of temporal bone on transcranial Doppler ultrasound beam shape. Ultrasound Med Biol 2000;26:239—44.
[6] Della Martina A, Meyer-Wiethe K, Allemann E, Seidel G. Ultrasound contrast agents for brain perfusion imaging and ischemic stroke therapy. J Neuroimaging 2005;15:217—32.
[7] Seidel G, Meairs S. Ultrasound contrast agents in ischemic stroke. Cerebrovasc Dis 2009;27(Suppl. 2):25—39.
[8] Wei K, Jayaweera AR, Firoozan S, Linka A, Skyba DM, Kaul S. Quantification of myocardial blood flow with ultrasound-induced destruction of microbubbles administered as a constant venous infusion. Circulation 1998;97:473—83.
[9] Rim SJ, Leong-Poi H, Lindner JR, Couture D, Ellegala D, Mason H, et al. Quantification of cerebral perfusion with ''Real-Time'' contrast-enhanced ultrasound. Circulation 2001;104:2582—7.
[10] Kern R, Diels A, Pettenpohl J, Kablau M, Brade J, Hennerici MG, et al. Real-time ultrasound brain perfusion imaging with analysis of microbubble replenishment in acute MCA stroke. J Cereb Blood Flow Metab 2011;31:1716—24.
[11] Bokor D, Chambers JB, Rees PJ, Mant TG, Luzzani F, Spinazzi A. Clinical safety of SonoVue, a new contrast agent for ultrasound imaging, in healthy volunteers and in patients with chronic obstructive pulmonary disease. Invest Radiol 2001;36: 104—9.
[12] Nedelmann M, Stolz E, Gerriets T, Baumgartner RW, Malferrari G, Seidel G, et al. Consensus recommendations for transcranial color-coded duplex sonography for the assessment of intracranial arteries in clinical trials on acute stroke. Stroke 2009;40:3238—44.